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Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv)) for US only

Published:

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

A3

8

WO 2004/013158

(54) Title: MUTANTS OF IgE PROTEINS AND USES THEREOF

(57) Abstract: The present invention generally relates to mutant IgE proteins. Specifically, the present invention relates to modified IgE proteins that have reduced flexibility in their heavy chains in comparison to unmodified IgE proteins and are, as a result, constrained in a particular conformational state. The present invention also relates to three-dimensional models of IgE glycosylation mutants. The present invention also relates to the use of proteins of the instant invention to produce and isolate compounds that will inhibit the binding of IgE protein to Fc ϵ R I or Fc ϵ R $\text{I}\alpha$. Also included in the present invention are nucleic acid molecules encoding proteins of the instant invention. Also included are compounds which inhibit the binding of IgE to its receptor. The present invention also includes therapeutic compositions and kits comprising proteins and/or compounds of the instant invention as well as methods of treating an animal using such compositions and kits.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/24336

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07K 16/00; C07H 21/04; C12N 15/00; A61K 39/395

US CL : 530/387.1, 387.3; 536/23.53; 435/69.1, 69.6; 424/130.1, 133.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/387.1, 387.3; 536/23.53; 435/69.1, 69.6; 424/130.1, 133.1.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| Y | WURZBURG, B.A. et al. Structure of the human IgE-Fc Cepsilon3-Cepsilon4 reveals conformational flexibility in the antibody effector domains. Immunity. September 2000, Vol. 13, pages 375-385, see entire document. | 1-7. |
| Y | GARMAN, S.C. et al. Structure of the Fc fragment of human IgE bound to its high-affinity receptor FcepsilonRIalpha. Nature. July 2000, Vol. 406, pages 259-266, see entire document. | 1-7. |
| X | HENRY, A.J. et al. Participation of the N-terminal region of Cepsilon3 in the binding of human IgE to its high-affinity receptor FcepsilonRI. Biochemistry. 1997, Vol. 36, pages 15568-15578, see entire document, particularly abstract and pages 15576-15578 and page 15572, left column. | 1 |
| Y | US 6,299,875 B1 (CAPLAN et al) 09 October 2001 (09.10.2001), see entire document. | 2-7 |
| Y | SENO, M. et al. Molecular cloning and nucleotide sequencing of human immunoglobulin E chain cDNA. Nucleic Acids Research. 1983, Vol. 11, No. 3, pages 719-726. See Figure 3. | 1-7. |
| | | 1 |



Further documents are listed in the continuation of Box C.



See patent family annex.

| | | |
|---|-----|--|
| * Special categories of cited documents: | "T" | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| "A" document defining the general state of the art which is not considered to be of particular relevance | "X" | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| "E" earlier application or patent published on or after the international filing date | "Y" | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "&" | document member of the same patent family |
| "O" document referring to an oral disclosure, use, exhibition or other means | | |
| "P" document published prior to the international filing date but later than the priority date claimed | | |

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/24336

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-8 and 22

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This International Search Authority has found 6 inventions claimed in the International Application covered by the claims indicated below:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-8 and 22, drawn to an isolated mutant IgE protein.

Group II, claims 9-12, drawn to an isolated nucleic acid molecule.

Group III, claims 13-15, drawn to an isolated protein.

Group IV, claims 16-17, drawn to a method to identify a compound that inhibits the binding of IgE to a FcERI.

Group V, claims 18-20, drawn to an isolated compound that inhibits the binding of IgE to an FcERI.

Group VI, claim 21, drawn to a method to protect an animal from an IgE mediated disease.

1. This International Search Authority considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated below:

The inventions listed as Groups I-V do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The technical feature linking groups I-V appears to be that they all relate to IgE proteins and mutants thereof.

However, Henry et al (Biochemistry, 1997, 36: 15568-15578) teaches human IgE comprising the amino acid sequence of SEQ ID NO:11 and mutant IgE proteins (see entire document).

Therefore, the technical feature linking the inventions of groups I-VI does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.

The special technical feature of Group I is considered to be a mutant IgE protein.

The special technical feature of Group II is considered to be DNA encoding an IgE protein.

The special technical feature of Group III is considered to be an isolated protein that binds to an antibody raised against a protein having the amino acid sequence of SEQ ID NO: 11.

The special technical feature of Group IV is considered to be a method of identifying a compound that inhibits binding of IgE to a FcERI.

The special technical feature of Group V is considered to be a compound that inhibits the binding of IgE to an FcERI.

The special technical feature of Group VI is considered to be a method to protect an animal from an IgE mediated disease.

Accordingly, Groups I-VI are not so linked by the same or corresponding technical feature as to form a single general inventive concept.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

INTERNATIONAL SEARCH REPORT

PCT/US03/24336

Continuation of B. FIELDS SEARCHED Item 3:

WEST, Medline, Biosis, EMBASE, CAPLUS, issued and published patents, Swissprot, SPTREMBL, Geneseq, PIR 78.
Search terms: SEQ ID NOS:11, 13, 15, 17, 19, 21, 23, 25, 27, IgE, closed configuration, mutant, inventor search.